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Effects of curcumin and its nano-micelle formulation on body weight, insulin resistance, adiponectin, and blood biochemical parameters of streptozotocin-induced diabetic rats

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ABSTRACT

The effects of curcumin and its nano-micelle form on body weight, insulin resistance, adiponectin, and blood biochemical parameters of streptozotocin-induced diabetic rats were studied. Diabetes was induced in fifty male Wistar rats which were divided into five groups treated with 1) no dietary supplements, 2 and 3) 40 and 80 mg curcumin/kg of feed, and 4 and 5) 40 and 80 mg nano-micelle curcumin/kg of feed. A group of ten untreated male Wistar rats was also considered a healthy control group. The serum concentrations of AST, ALT, glucose, insulin, triglycerides, cholesterol, HDL-C, LDL-C, and adiponectin, as well as insulin resistance, were assessed. Body weight and weight of liver, heart, and pancreas were also evaluated. Induction of diabetes increased the serum concentrations of AST, ALT, glucose, triglycerides, cholesterol, LDL-C, and insulin resistance and decreased the serum levels of insulin, adiponectin, and HDL-C, as well as body weight and weight of the heart and pancreas ($p < 0.05$). Nano-micelle form of curcumin alleviated the negative effects of glucose, lipid profile, and liver enzymes in diabetic rats ($p < 0.05$). In conclusion, the nano-micelle form of curcumin showed better efficiency compared to curcumin for improving the adverse effects of diabetes. It can be suggested that the nano-micelle form of curcumin at specific doses might be useful for diabetes treatment.

Keywords

curcumin, diabetes, hepatic enzymes, insulin resistance, nano-curcumin

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Abbreviations

AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
HOMA-IR: Homeostatic model assessment of insulin resistance
HDL: High-density lipoprotein
LDL: Low-density lipoprotein
T2DM: Type 2 diabetes mellitus

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Introduction

Diabetes is a big challenge for most people in the world and T2DM is known for insulin resistance, faulted glucose, lipid metabolism, and deficient insulin production [1]. Therefore, increased levels of fasting glucose and postprandial glucose are its consequences [2]. Insulin resistance is the first sign of T2DM in most individuals. For maintaining normal glucose levels, beta cells raise insulin secretion and the response is observed as hyperinsulinemia. When hyperinsulinemia in patients cannot maintain normoglycemia, fasting blood glucose and glucose tolerance are faulted [3]. Faulted fasting blood glucose progresses to T2DM [4]. Several factors, such as glucotoxicity, lipotoxicity, inflammation, and accumulation of amyloid disturb beta-cell function [2]. Problematic lipid and glucose metabolism promote the pathogenesis of T2DM [4]. Adiponectin, an insulin-sensitizing hormone with anti-apoptotic and anti-inflammatory effects, is produced in adipose tissues and its levels decline in patients with T2DM [5]. The serum concentrations of AST and ALT increase in diabetes [6]. Augmented levels of these enzymes show hepatic injury in both the hepatocellular cytosol and mitochondria [7]. Increased ALT and AST are strongly correlated with insulin resistance and T2DM [8].

The control and management of diabetes are challenges for the medical system. Different manipulations are used for the treatment of diabetes, such as anti-diabetic medications and lifestyle intervention [9] (healthy nutrition and daily physical activity). The use of synthetic compounds may induce severe side effects, including hypoglycemic coma and hepatorenal disorders [9]. Medicinal plant supplements are recommended with high potency for preventing and managing T2DM [10-13]. Curcumin is an active molecule in the rhizome of turmeric. It has antioxidant, anti-inflammatory, anti-microbial, immunomodulatory, hypoglycaemic, and anti-rheumatic effects [14, 15]. Curcumin controls glycemia and lipidaemia in the body [16] and can be used as an appropriate compound for diabetes treatment. The use of natural isolates from plants is an appropriate strategy for the treatment of different disorders. However, curcumin users face major limitations due to formulation, application, and degradation during processing [17, 18]. Using the nano-micelle form of curcumin may prevent its degradation during processing and digestion and helps to increase its efficiency. Therefore, this study was conducted to investigate the effects of curcumin and its nano-micelle form on body weight, insulin resistance, adiponectin secretion, and blood biochemical parameters of streptozotocin-induced diabetic rats.

Results

The effects of treatments on the serum concentrations of glucose, insulin, adiponectin, and insulin resistance of the rats are shown in Figure 1. The results showed that diabetes induction increased the serum concentration of glucose ($p < 0.0001$) and decreased the serum levels of insulin ($p < 0.0001$), HOMA-IR ($p < 0.0001$), and adiponectin ($p < 0.0001$). Our findings indicated that the administration of curcumin at the level of 40 mg/kg of rat diet and nano-micelle curcumin in both doses reduced the serum concentrations of glucose ($p < 0.05$) and raised insulin ($p < 0.05$), HOMA-IR ($p < 0.05$), and adiponectin ($p < 0.05$). The best responses were observed in nano-micelle curcumin groups, especially in the rats which received 80 mg/kg of diet ($p < 0.05$).

The effects of treatments on the serum lipid profile of the rats are presented in Table 1. The results of the present study revealed that the induction of diabetes significantly increased the serum concentrations of triglycerides ($p < 0.0001$), cholesterol ($p < 0.0001$), and LDL-C ($p < 0.0001$) and diminished HDL-C ($p < 0.0001$). Administration of curcumin had no significant effect compared to the control group ($p > 0.05$). The administration of nano-micelle curcumin decreased the serum levels of triglycerides ($p < 0.0001$), cholesterol ($p < 0.0001$), and LDL-C ($p < 0.0001$) and increased HDL-C ($p < 0.0001$). No significant difference was observed between the nano-treatments ($p > 0.05$).

The effects of treatments on body weight and relative percentages of pancreas, heart, and liver of the diabetic rats are shown in Table 2. Our results showed that diabetes induction reduced body weight ($p < 0.0001$) and the relative weight of pancreas ($p < 0.05$) and heart ($p < 0.05$), but did not have any significant effect on the liver weight ($p > 0.05$). The results did not show any significant differences between diabetic treatments for the relative weight of the pancreas and heart. Supplementing 40 mg curcumin/kg of feed decreased body weight compared to the diabetic control group ($p < 0.05$).

The effects of treatments on serum levels of the liver enzymes of diabetic rats are shown in Table 3. Induction of diabetes raised the serum concentrations of ALT and AST ($p < 0.0001$). The current research demonstrated that nano-curcumin administration at both doses decreased the serum concentrations of ALT and AST ($p < 0.0001$). Serum ALT was not affected by 40 and 80 mg curcumin/kg of feed ($p > 0.05$).

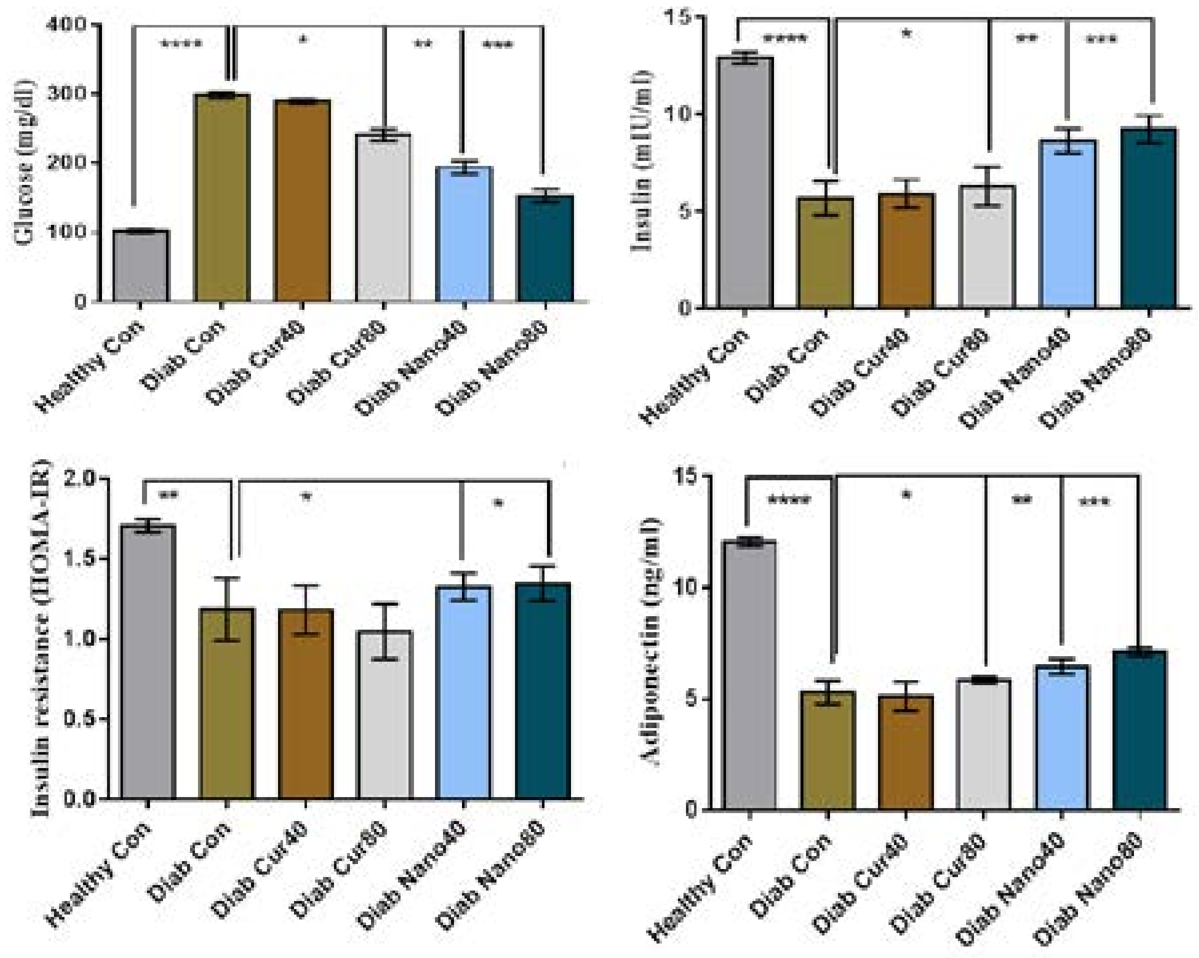

Figure 1.
Effects of experimental treatments on the serum concentrations of glucose, insulin, adiponectin, and insulin resistance of the diabetic rats. *, **, ***, and **** show significant differences at 0.05, 0.01, 0.001, and 0.0001, respectively. Cur: Curcumin; Nano: nano-curcumin; Healthy Con: Healthy control rats; Diab Con: Diabetic Control rats with no dietary supplement; Diab Cur40, Diab Cur80, Diab Nano40, and Diab Nano80 are 40 and 80 mg curcumin and nano-micelle curcumin/kg of feed, respectively.
HOMA-IR: Homeostatic model assessment of insulin resistance index was measured based on the product of fasting serum glucose concentration (mmol/l) and fasting blood serum insulin concentration (μU/ml) divided by the constant 5.22×18 as reported by Mathews et al. [20].

Table 1.
Effects of treatments on the serum lipid profile (mg/dl) of the diabetic rats

	Triglycerides	Cholesterol	HDL-C	LDL-C
Healthy Control	50.20 ± 5.49^c	116.60 ± 4.21^c	52.80 ± 3.96^a	53.76 ± 7.08^c
Diabetic Control	89.60 ± 3.64^a	185.60 ± 8.56^a	26.75 ± 1.50^c	142.10 ± 8.41^a
Diabetic Cur40	89.00 ± 3.74^a	182.40 ± 2.51^a	26.20 ± 2.28^c	138.40 ± 4.36^a
Diabetic Cur80	88.60 ± 3.78^a	179.80 ± 2.58^a	28.60 ± 2.60^c	133.50 ± 4.50^a
Diabetic Nano40	82.80 ± 3.56^b	171.60 ± 2.07^b	32.75 ± 2.07^b	122.20 ± 2.12^b
Diabetic Nano80	81.20 ± 2.77^b	166.40 ± 2.96^b	34.20 ± 2.68^b	116.00 ± 3.90^b
P-value	0.000	0.000	0.000	0.000
SEM	**2.640**	**4.420**	**1.850**	**5.960**

$^{a-c}$ Means in each column with different superscripts are significantly different ($p < 0.05$). SEM: Standard error of means. Curcumin (Cur) and nano-micelle curcumin (Nano) with specified doses of 40 and 80 mg/kg diet. HDL-C, high density lipoprotein-cholesterol, LDL-C, low density lipoprotein-cholesterol.

Table 2.
Effects of treatments on body weight (g) and the relative weights (w/w*100) of the pancreas, heart, and liver of the diabetic rats

	Body weight	Pancreas	Heart	Liver
Healthy Control	308.80 ± 16.65^{a}	0.51 ± 0.35^{a}	1.18 ± 0.04^{a}	10.04 ± 0.45
Diabetic Control	224.60 ± 3.71^{b}	0.23 ± 0.02^{b}	0.98 ± 0.03^{b}	10.22 ± 1.16
Diabetic Cur40	191.00 ± 27.48^{c}	0.36 ± 0.06^{ab}	0.90 ± 0.13^{b}	10.37 ± 2.50
Diabetic Cur80	243.40 ± 53.90^{b}	0.40 ± 0.19^{ab}	0.89 ± 0.10^{b}	10.59 ± 1.13
Diabetic Nano40	209.00 ± 15.17^{bc}	0.35 ± 0.04^{b}	0.87 ± 0.06^{b}	11.13 ± 0.90
Diabetic Nano80	225.00 ± 15.00^{bc}	0.42 ± 0.09^{ab}	0.85 ± 0.03^{b}	10.34 ± 1.07
P-value	0.000	0.013	0.000	0.848
SEM	**8.250**	**0.023**	**0.024**	**0.023**

$^{a-c}$ Means in each column with different superscripts are significantly different ($p < 0.05$). SEM: Standard error of means. Curcumin (Cur) and nano-micelle curcumin (Nano) with specified doses of 40 and 80 mg/kg diet.

Discussion

The results of the present study showed that the induction of diabetes increased the level of glucose and decreased insulin. The latter findings have already been reported by others [1-3]. Diabetes destroys beta-cells and hereby increases blood glucose levels and decreases insulin concentrations. Our results revealed that the oral administration of 80 mg curcumin and nano-curcumin/kg of feed reduced the glucose level and raised serum insulin concentration. The difference between curcumin 40 and control diabetic groups was not significant. It means that nano-curcumin can alleviate the adverse effects of diabetes on glucose and insulin levels. Curcumin is known to have an anti-hyperglycaemic effect in diabetic subjects [21-23]. Previous studies indicated that the administration of curcumin improved insulin sensitivity by reducing glycemia and dyslipidemia in rats when they are fed a high-fat diet [24-26]. In agreement with the results of the current study, Lu et al. [27] showed that curcumin supplementation improved glucose and insulin intolerance by activating the 5'-adenosine monophosphate-activated protein kinase pathway in diabetic animals. Administration of nano-micelle curcumin showed a better response compared to curcumin. Low absorption rate and rapid degradation of curcumin in the intestinal system have been reported [28]. utilizing the nano-micelle structure of curcumin prevents rapid degradation and promotes absorption in the intestinal system, leading to better anti-hyperglycaemic function. Diabetes may destroy pancreas function and insulin secretion because it disturbs the oxidant-antioxidant balance. It seems that using the nano-micelle form of curcumin increases antioxidant properties and prevents pancreas injury. Therefore, the administration of nano-micelle curcumin decreases the level of glucose and subsequently reduces the serum concentration of insulin. As observed in the current study, insulin resistance improves following improved insulin concentration and pancreas injury.

Table 3.
Effects of treatments on the serum levels of the liver enzymes of the diabetic rats

Treatments	ALT	AST
Healthy Control	22.11±0.84c	320.90±0.97e
Diabetic Control	37.58±0.49a	381.60±5.90a
Diabetic Cur40	36.62±0.49a	370.60±5.39b
Diabetic Cur80	36.02±0.44a	363.80±2.55b
Diabetic Nano40	35.36±0.83b	350.20±4.71c
Diabetic Nano80	34.64±1.14b	334.60±1.14d
p-value	0.000	0.000
SEM	0.980	3.930

$^{a-e}$ Means in each column with different superscripts are significantly different ($p < 0.05$). SEM: Standard error of means. Curcumin (Cur) and nano-micelle curcumin (Nano) with specified doses of 40 and 80 mg/kg diet. ALT: alanine aminotransferase; AST: aspartate aminotransferase.

The results showed that diabetes decreased adiponectin. However, curcumin administration at a higher dose and nano-micelle form as 40 and 80 mg/kg of feed raised the level of adiponectin, and the best response was observed in the rats fed nano-micelle curcumin. Adiponectin is produced in the adipose tissue, and its tissue levels directly correlate with its function. Adiponectin is an insulin-sensitizing hormone with anti-apoptotic and anti-inflammatory effects. Adiponectin declines in the adipose tissues of patients with T2DM [5]. Curcumin corrects the improper function of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB) in adipocytes and may improve adiponectin levels [29]. NF-kB links to cancer, inflammatory conditions, autoimmune diseases, and improper immune development. It controls the transcription of DNA, cytokine production, and cell survival. It is well-known that NF-kB regulates inflammatory responses [30]. Our findings showed a direct relationship between insulin and adiponectin. It means that the administration of curcumin increases insulin levels and subsequently augmented adiponectin levels. Diabetes increased the concentration of triglycerides, cholesterol, and LDL-C, and decreased HDL-C. Exclusively the administration of nano-curcumin could improve the serum lipid profile of rats. Diabetes disturbs lipid metabolism [1] and nano-curcumin improved blood lipid profile in diabetic rats compared to the control group. These results are consistent with the previous findings [29, 31]. Improved lipid profile could be attributed to the rise in lipoprotein lipase activity that reduces serum triglycerides. Moreover, diabetes induces lipid peroxidation and increases triglycerides, cholesterol, and LDL-C. Curcumin diminishes lipid peroxidation by normalizing the levels of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase [31]. The administration of the nano-structure of curcumin spares antioxidant enzymes and improves antioxidant properties, thereby improving the lipid profile.

Induction of diabetes increased the level of liver enzymes, and administration of curcumin decreased their activities. The increased levels of transaminase enzymes, namely ALT and AST, are directly associated with liver cell damage. Augmented levels of these enzymes show hepatic injury in the hepatocellular cytosol and mitochondria [7]. On the other hand, a rise in ALT and AST by curcumin has already been reported in T2DM [8]. Curcumin protects liver hepatocytes against oxidative injuries and decreases the level of antioxidant enzymes.

The current study showed that diabetes decreased body weight, as well as pancreas and heart weight, and administration of curcumin at the level of 80 alleviated the adverse effects of diabetes on pancreas weight. It has been reported that diabetes reduces body weight [32, 33]. Diabetes decreases energy and body weight, increases urinary excretion and catabolic processes [34], and damages the pancreas. Curcumin in any form could not alleviate the adverse effects of diabetes on body weight. Hodaei et al. [35] showed that curcumin supplementation did not improve body weight in patients with T2DM. Consumption of curcumin decreased body weight in patients with metabolic syndrome [36]. It seems that more time was needed to recover the body weight or organ weights disrupted by streptozotocin injection in rats. However, the weight of the pancreas partly improved. It might be needed to optimize the level and time of curcumin or nano-micelle curcumin administration, or diabetes inducers, such as streptozotocin. It is urgently needed to lower the glucose level of diabetic subjects, and protect their endocrine/exocrine secretion balance and curcumin in all cases showed positive effects on adiponectin, ALT, or AST levels. Further research is required to clarify the suitable doses of curcumin and nano-micelle curcumin along with other nutrients in diabetic subjects.

In conclusion, diabetes-induced damage to the pancreas increased the serum glucose, lipid profile, and insulin resistance and decreased adiponectin, liver enzymes, body weight, and pancreas weight. Administration of the nano-micelle form of curcumin improved insulin resistance and the serum concentrations of glucose, insulin, lipid profile, adiponectin, and liver enzymes. It is suggested that curcumin nano-micelle might be effective for diabetic patients with special attention to doses.

Materials and Methods

Experimental animals

All the used procedures were approved by the Ethics Committee of Ferdowsi University of Mashhad, Iran (No: 3.44995). A total number of 60 male Wistar rats with a mean weight of 180-200 g and 60 days of age were purchased from the Pasture Institute (Tehran, Iran). The animals were kept in standard individual cages for 49 days (7 days of adaptation and 42 days of study) under a 12L:12D lighting cycle at 20 ºC-25 ºC. The animals had free access to standard pellet feed and fresh water. Feed was prepared from Javaneh Khorasan Company (Mashhad, Iran).

Preparation of curcumin and nano-micelle curcumin

Pure turmeric rhizome extract as the powder was purchased from Sami Lab Limited (Bengaluru, Karnataka, India). The powder contained 79.4% curcumin, 17.6% demethoxycurcumin, and 3% bisdemethoxycurcumin. Nano-micelle form of this extract as nano-micelle curcumin was purchased from Exir Nano Sina Co. (Tehran, Iran, IRC: 1228225765). The measured size of nano-micelle curcumin was about 10 nm as described by Hatamipour et al. [19].

Induction of diabetes

At the beginning of the study, diabetes was induced in 50 male Wistar rats by one dose of intraperitoneal streptozotocin (Sigma, St. Louis, MO, USA) (60 mg/kg body weight) in 0.05 M cold citrate buffer (pH 4.5) for the overnight fasted rats. To stabilize streptozotocin in an aqueous media, cold citrate buffer was

used. A group of 10 rats was not treated with streptozotocin and considered healthy control animals. An Accu-chek blood glucose meter (Roche Diagnostics) was used for monitoring fasting blood glucose. The rats with fasting blood glucose higher than 250 mg/dl for five consecutive days after the administration of streptozotocin were considered diabetic rats.

Following diabetes induction, the animals were divided into five groups and received no dietary supplement of curcumin or nano-micelle curcumin (Diab-Con), 40 mg curcumin/kg of pelleted feed (Diab-Cur40), 80 mg curcumin/kg of pelleted feed (Diab-Cur80), 40 mg nano-micelle curcumin/kg of pelleted feed (Diab-Nano40), and 80 mg nano-micelle curcumin/kg of pelleted feed (Diab-Nano80). A group of 10 rats was considered a healthy control and did not receive any streptozotocin or curcumin forms (Healthy-Con). All formulations were fed to rats for 42 days.

Body and organ weight

At the end of the experiment, the animals were weighed and then euthanized by CO_2. Weights of the liver, heart, and pancreas were calculated as the percentage of live body weight.

Blood biochemical parameters

At the end of the study and after 12 h fasting, blood samples were collected from the left ventricle, centrifuged at 2500 RPM for 15 min, stored at -20ºC, and investigated for blood biochemical parameters. The serum concentrations of AST, ALT, glucose, insulin, triglycerides, cholesterol, HDL-C, and LDL-C were evaluated by an enzyme-linked immunosorbent assay commercial kit (Pars Azmoon, Tehran, Iran). HOMA-IR index was measured based on the fasting serum glucose concentration (mmol/l) and the fasting blood serum insulin concentration (µU/ml) divided by the constant 5.22×18 as reported by Matthews et al. [20]. The level of adiponectin was assessed by commercial kits (Otsuka Pharmaceutical Co., Tokyo, Japan).

Data analysis

The obtained data were analyzed by the SPSS software version 24 and the significance was designated at $p < 0.05$ for the differences between the six groups for all studied parameters. The differences between all the studied groups were evaluated by a one-way analysis of variance.

Authors' Contributions

H.D. performed the experiment and wrote the main manuscript. H.K. contributed to the experiment as supervisor and corresponding author. M.R.J. and A.J. contributed to the manuscript as advisors.

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Competing Interests

The authors declare that there is no conflict of interest.

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